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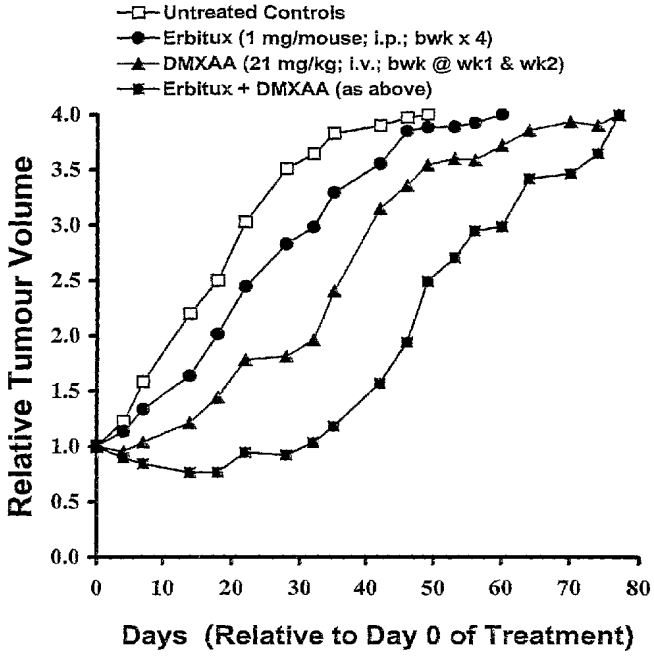
(54) Title: COMBINATIONS COMPRISING DMXAA FOR THE TREATMENT OF CANCER



(57) Abstract: The present invention relates to combinations of the xanthenone acetic acids class such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA) and EGFR signalling pathway inhibitors. More particularly, the invention is concerned with the use of such combinations in the treatment of cancer and pharmaceutical compositions containing such combinations.

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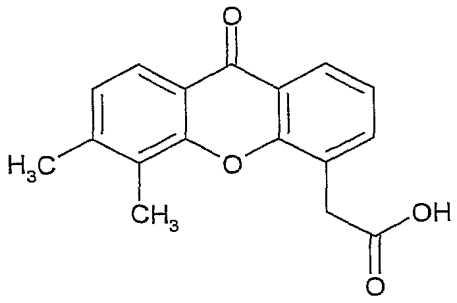
COMBINATIONS COMPRISING DMXAA FOR THE TREATMENT OF CANCER

The present invention relates to combinations of compounds of the class having the formula (I) as defined below, for example compounds of the xanthenone acetic acid class having the formula (II) as defined below, such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA), or a pharmaceutically acceptable salt, ester or prodrug thereof and EGFR signalling pathway inhibitors. For example, the present invention relates to synergistic combinations of compounds of the class having the formula (I) as defined below, for example compounds of the xanthenone acetic acid class having the formula (II) as defined below, such as 5,6-dimethylxanthenone-4-acetic acid (DMXAA), or a pharmaceutically acceptable salt, ester or prodrug thereof and EGFR signalling pathway inhibitors. More particularly, the invention is concerned with the use of such combinations in the treatment of cancer. The present invention also relates to pharmaceutical compositions containing such combinations.

5,6-dimethylxanthenone-4-acetic acid (DMXAA) is represented by the following formula:



Three phase I clinical trials of DMXAA as a monotherapy have recently been completed, with dynamic MRI showing that it induces a significant reduction in tumour blood flow at well-tolerated doses. DMXAA is thus one of the first vascular disrupting agents (VDAs) for which activity (irreversible inhibition of tumour blood flow) has been documented in human tumours. These findings are in agreement with preclinical studies using syngeneic murine tumours or human tumour xenografts, which showed that its antivascular activity produced prolonged inhibition of tumour blood flow leading to extensive regions of haemorrhagic necrosis.

However, in these phase I clinical trials of DMXAA there were very few tumour responses, demonstrating that DMXAA alone does not have significant potential in cancer treatment as a single agent. Therefore, there is a need to identify compounds that could have a synergistic effect with DMXAA.

There is a new class of cancer drugs available that are not cytotoxics, but block the epidermal growth factor signalling pathways. Examples include Erbitux™ (cetuximab), a monoclonal antibody binding to epidermal growth factor receptor (EGFR) and Tarceva™ (erlotinib) and Iressa™ (gefitinib), small molecules that inhibit cell signalling in the EGFR pathway. We have surprisingly found that DMXAA may act synergistically with these new agents, enhancing their anti-cancer activity.

EGFR signalling pathway inhibitors

Tumours have been found to overexpress certain growth factors that enable them to proliferate rapidly, one of which is EGF. Activation of EGFR by binding of EGF and formation of an active receptor dimer induces phosphorylation of the tyrosine kinase in the intracellular domain of the receptor. The ras protein initiates a cascade of phosphorylations which result in activation of mitogen activated protein kinase (MAPK). MAPK triggers events in the nucleus that result in cell division. As a result, overexpression of EGF, or of EGFR on the cell surface can result in uncontrolled cell division characteristic of cancer. Expression levels of EGF and EGFR are negatively correlated with prognosis and survival in cancer, and inhibiting the signalling pathway has been shown to improve survival.

The EGFR pathway is targeted by Erbitux™ (cetuximab, a chimeric monoclonal antibody marketed for colorectal cancer by Imclone and Bristol-Myers Squibb in the US and Schering in Europe), which binds to EGF receptors, blocking EGF from binding to them. Tarceva™ (erlotinib, marketed by Genentech and OSI Pharmaceuticals in the US and Roche elsewhere) and Iressa™ (gefitinib, marketed by AstraZeneca), small molecules marketed for non-small cell lung cancer, inhibit phosphorylation of the intracellular tyrosine kinase, interfering with cell signalling.

This limits the uncontrolled cell division caused by overstimulation of the EGFR signalling pathway.

Of the EGFR signalling pathway inhibitors, only Tarceva™ has demonstrated a survival advantage in phase III trials, with both Erbitux™ and Iressa™ being approved based on tumour response rates. Since its approval Iressa™ has completed a number of phase III trials, which found that it did not extend median survival, despite the improvement in response rate over standard care.

Previous EGFR signalling pathway inhibitor combination studies

Clinical trials of the EGFR signalling pathway inhibitors do not suggest that they are likely to show synergy with vascular targeting anti-cancer agents. Erbitux™ is approved for use as a monotherapy or in combination with irinotecan, a non-vascular targeting cytotoxic.

Both Iressa™ and Tarceva™ have been tested with combinations that include paclitaxel, a compound known to have anti-angiogenic properties secondary to its cytotoxic activity, with no evidence of benefit. For both products, two trials failed to show a benefit of adding the EGFR signalling inhibitor to standard chemotherapy. Iressa™ is indicated only as a monotherapy because two large, controlled, randomised trials showed it to give no survival benefit when used first-line in combination with chemotherapy that included a platin and another agent, which could be paclitaxel. Tarceva™ has been similarly unsuccessful in demonstrating a survival benefit when combined with carboplatin/paclitaxel or cisplatin/gemcitabine. Tarceva™ has demonstrated a survival benefit in pancreatic cancer patients when combined with gemcitabine, a non-vascular targeting cytotoxic cancer drug.

Previous DMXAA combination studies

DMXAA has previously been demonstrated to have synergy with a number of agents in xenograft studies. These agents include widely used cytotoxic chemotherapies such as taxanes (paclitaxel and docetaxel), platins (cisplatin and carboplatin), vinca

alkaloids (vincristine), antimetabolites (gemcitabine), topoisomerase II inhibitors (etoposide) and anthracyclines (doxorubicin). It is believed that the synergy arises because DMXAA causes necrosis in the centre of tumours, but seems to leave a viable rim of cancer cells. These are targeted by the cytotoxic agents which primarily act on rapidly proliferating cells. None of these chemotherapy agents are known to affect the EGFR signalling pathway.

DMXAA is currently in two phase II trials examining its anti-tumour efficacy in combination with paclitaxel and carboplatin, and one trial combining it with docetaxel. The cytotoxic effect of the taxanes is caused by interference with tubulin, which prevents normal mitosis (cell division). A secondary effect is disruption of newly formed blood vessels, since the cells of the new vascular endothelium depend on tubulin to maintain their shape. However, the cytotoxic effect is overriding at higher doses, such as those used in chemotherapy. Any synergy between DMXAA and the taxanes is thought to be a result of the targeting of different parts of the tumour, as described above.

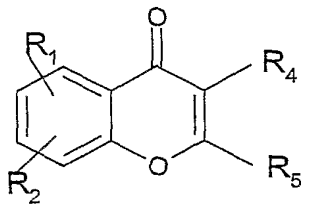
Other agents have also been shown to enhance the activity of DMXAA in xenograft studies. Although the exact mechanism of action of DMXAA is not understood, it is believed to cause upregulation of various cytokines, and compounds with similar activity appear to enhance its effectiveness. These include tumour necrosis factor stimulating compounds and immunomodulatory compounds such as intracellular adhesion molecules (ICAMs).

Diclofenac, an NSAID that has been shown to enhance the anti-tumour activity of DMXAA, is believed to affect the PK of DMXAA via competition for metabolic pathways. At a concentration of 100μM, diclofenac has been shown to significantly inhibit glucoronidation (>70%) and 6-methylhydroxylation (>54%) of DMXAA in mouse and human liver microsomes. *In vivo*, diclofenac (100mg/kg i.p.) has been shown to result in a 24% and 31% increase in the plasma DMXAA AUC (area under the plasma concentration-time curve) and a threefold increase in $T_{1/2}$ ($P<0.05$) in male and female mice respectively (see Zhou *et al.* (2001) *Cancer Chemother. Pharmacol.* **47**, 319-326). Other NSAIDs have been shown to have a similar effect.

Similarly to diclofenac, thalidomide, which is approved for erythema nodosum leprosum (ENL), seems to enhance the activity of DMXAA. Thalidomide is also known to have anti-angiogenic effects but the synergy is caused by effect on metabolism of DMXAA. It competes for glucuronidation, prolonging DMXAA's presence at therapeutic levels in tumour tissue. Thalidomide increases the AUC of DMXAA by 1.8 times in plasma, liver and spleen and by three times in tumour (see Kestell *et al.* (2000) *Cancer Chemother. Pharmacol.* **46**(2), 135-41).

Description of the invention

In a first aspect, the present invention provides a method for modulating neoplastic growth, which comprises administering to a mammal, including a human, in need of treatment an effective amount of formula (I):



Formula (I)

wherein:

(a) R_4 and R_5 together with the carbon atoms to which they are joined, form a 6-membered aromatic ring having a substituent $-R_3$ and a radical $-(B)-COOH$ where B is a linear or branched substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated, and wherein R_1, R_2 and R_3 are each independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, CF_3, CN, NO_2, NH_2, OH, OR, NHCOR, $NHSO_2R$, SR, SO_2R or NHR, wherein each R is independently C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy; or

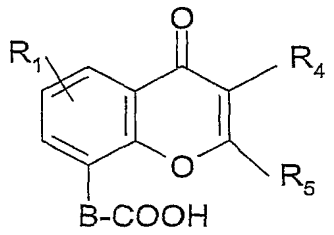
(b) one of R_4 and R_5 is H or a phenyl radical, and the other of R_4 and R_5 is H or a phenyl radical which may optionally be substituted, thenyl, furyl, naphthyl, a C_1-C_6 alkyl, cycloalkyl, or aralkyl radical; R_1 is H or a C_1-C_6 alkyl or C_1-C_6 alkoxy radical; R_2 is the radical -(B)-COOH where B is a linear or branched

substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated,

or a pharmaceutically acceptable salt, ester or prodrug thereof and concomitantly or sequentially administering an EGFR signalling pathway inhibitor.

Where (B) in the radical -(B)-COOH is a substituted C_1-C_6 alkylene radical, the substituents may be alkyl, for example methyl, ethyl, propyl or isopropyl, or halide such as fluoro, chloro or bromo groups. In one example the substituent is methyl.

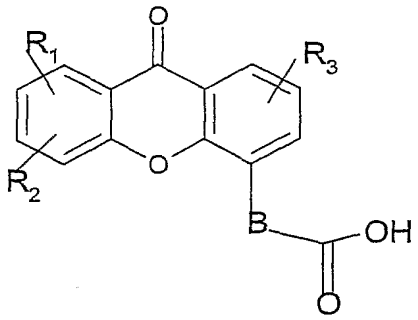
In one embodiment of the first aspect of the invention, the compound of the formula (I) as defined above may be a compound of the formula (II):



Formula (II)

where R_1, R_4, R_5 and B are as defined above for formula (I) in part (b).

In a further embodiment of the first aspect of the invention, the compound of formula (I) as defined above may be a compound of the formula (III):



Formula (III)

wherein R_1, R_2 and R_3 are each independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, CF_3, CN, NO_2, NH_2, OH, OR, NHCOR, $NHSO_2R$, SR, SO_2R or

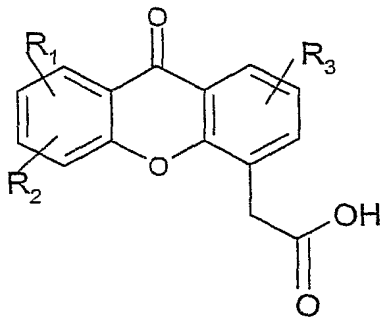
NHR, wherein each R is independently C_1–C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy;

wherein B is as defined for formula (I) above;

and wherein in each of the carbocyclic aromatic rings in formula (I), up to two of the methine (-CH=) groups may be replaced by an aza (-N=) group;

and wherein any two of R_1, R_2 and R_3 may additionally together represent the group -CH=CH-CH=CH-, such that this group, together with the carbon or nitrogen atoms to which it is attached, forms a fused 6-membered aromatic ring.

For example, the compound of formula (III) may be a compound of the formula (IV):

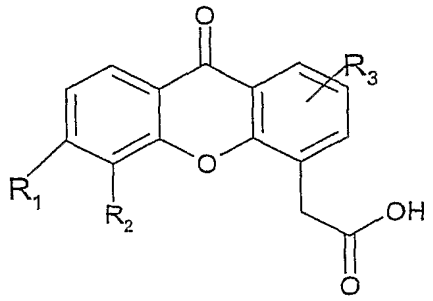


Formula (IV)

wherein R, R_1, R_2 and R_3 are as defined for formula (III).

In one embodiment of the compound of formula (IV), R_2 is H, one of R_1 and R_3 is selected from the group consisting of C_1-C_6 alkyl, halogen, CF_3, CN, NO_2, NH_2, OH, OR, NHCOR, $NHSO_2R$, SR, SO_2R or NHR, wherein each R is independently C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy, and the other of R_1 and R_3 is H.

For example, the compound of formula (IV) may be of the formula (V):



Formula (V)

wherein R, R_1, R_2 and R_3 are as defined for formula (IV).

The compound of formula (V) may be, for example, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), or a pharmaceutically acceptable salt, ester or prodrug thereof.

In one embodiment of the invention the EGFR signalling pathway inhibitor is a monoclonal antibody.

In one embodiment of the invention the EGFR signalling pathway inhibitor is Erbitux™ (cetuximab).

In one embodiment of the invention the EGFR signalling pathway inhibitor is a tyrosine kinase inhibitor.

In one embodiment of the invention the EGFR signalling pathway inhibitor is Tarceva™ (erlotinib).

In one embodiment of the invention the EGFR signalling pathway inhibitor is Iressa™ (gefitinib).

In another aspect, the present invention provides the use of a EGFR signalling pathway inhibitor for the manufacture of a medicament (e.g. of a unit dose of a medicament), for simultaneous, separate or sequential administration with the compound of formula (I) as defined above or a pharmaceutically acceptable salt, ester or prodrug thereof (e.g. a unit dose of the compound of formula (I) as defined above

or a pharmaceutically acceptable salt, ester or prodrug thereof), for the modulation of neoplastic growth.

In another aspect, the present invention provides the use of the compound of formula (I) as defined above or a pharmaceutically acceptable salt, ester or prodrug thereof for the manufacture of a medicament (e.g. a unit dose of a medicament) for simultaneous, separate or sequential administration with the EGFR signalling pathway inhibitor (e.g. a unit dose of the EGFR signalling pathway inhibitor) for the modulation of neoplastic growth.

According to one aspect, the neoplastic growth is a tumour and/or a cancer.

In a further aspect, the neoplastic growth is one or more of ovarian, prostate, lung, pancreatic, colorectal, and head and neck cancer.

In a further aspect, there is provided a pharmaceutical formulation comprising a combination of the compound of formula (I) as defined above or a pharmaceutically acceptable salt, ester or prodrug thereof (e.g. in a unit dose) and an EGFR signalling pathway inhibitor (e.g. in a unit dose).

In one embodiment there is provided a compound according to formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof and an EGFR signalling pathway inhibitor for use (in combination) as a medicament for modulation of neoplastic growth.

The invention further provides a process for the preparation of a pharmaceutical formulation which process comprises bringing into association a combination of the compound of formula (I) as defined above or a pharmaceutically acceptable salt, ester or prodrug thereof (e.g. a unit dose of the compound of formula (I) as defined above or a pharmaceutically acceptable salt, ester or prodrug thereof) and an EGFR signalling pathway inhibitor (e.g. a unit dose of the EGFR signalling pathway inhibitor), optionally with one or more pharmaceutically acceptable carriers therefor. For example, the pharmaceutical formulation may be in a unit dose.

Pharmaceutical formulations comprise the active ingredients (that is, the combination of a compound of formula (I) as defined above or pharmaceutically acceptable salt, ester or prodrug thereof and the growth factor inhibitor, for example EGFR signalling pathway inhibitor), for example together with one or more pharmaceutically acceptable carriers therefor and optionally other therapeutic and/or prophylactic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients in the formulation and not deleterious to the recipient thereof.

The compound of formula (I) as defined above or a pharmaceutically acceptable salt, ester or prodrug thereof and the EGFR signalling pathway inhibitor may be administered simultaneously, separately or sequentially.

In one embodiment, the pharmaceutically acceptable salt is a sodium salt.

The amount of a combination of a compound of formula (I) as defined above or pharmaceutically acceptable salt, ester or prodrug thereof and an EGFR signalling pathway inhibitor required to be effective as a modulator of neoplastic growth will, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the mammal's bodyweight, age and general condition and the nature and severity of the disease to be treated.

A suitable effective dose of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for administration, simultaneously, separately or sequentially, with an EGFR signalling pathway inhibitor, for the treatment of cancer is in the range of 600 to 4900 mg/m^2. For example from 2500 to 4000 mg/m^2, from 1200 to 3500 mg/m^2, more suitably from 2000 to 3000 mg/m^2, particularly from 1200 to 2500 mg/m^2, more particularly from 2500 to 3500 mg/m^2, preferably from 2250 to 2750 mg/m^2.

It is of course also possible to base dosages upon the weight of a patient. For example, a dosage of a compound of formula (I) as defined above, or a pharmaceutically acceptable salt thereof, for administration, simultaneously, separately or sequentially,

with an EGFR signalling pathway inhibitor, for the treatment of cancer may be in the range of 15 to 125 mg/kg body weight may be administered. More preferably, the dosage is from 30 to 80 mg/kg, or 30 to 70 mg/kg.

In one embodiment the Erbitux™ may be administered in a loading dose of 250 to 500 mg/m^2 (e.g. about 400 mg/m^2) and then weekly doses of 150 to 350 mg/m^2 (e.g. about 250 mg/m^2).

As above, the dosage for Erbitux™ may be based upon the weight of a patient. For example, Erbitux™ may be administered in a loading dose of 6 to 13 mg/kg (e.g. about 10 mg/kg) and then weekly doses of 4 to 9 mg/kg (e.g. about 6 mg/kg).

In one embodiment the Iressa™ and Tarceva™ may be administered in an amount of one 100 to 350 mg tablet daily. For example, Iressa™ may be administered in an amount of one 250 mg tablet daily, and the Tarceva™ may be administered in an amount of one 150 mg tablet daily.

The pharmaceutical formulation may be delivered intravenously (e.g. a formulation containing Erbitux™) or orally (e.g. a formulation containing Iressa™ or Tarceva™). The pharmaceutical composition for intravenous administration may be used in the form of sterile aqueous solutions or in an oleaginous vehicle which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions may be buffered (e.g. to a pH from 3 to 9), if necessary.

The pharmaceutical formulations (e.g. containing Iressa™ or Tarceva™) may, for example, be administered orally in one or more of the forms of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications.

If the pharmaceutical formulation is a tablet, then the tablet may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or

tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid formulations of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compound may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

Pharmaceutical formulations suitable for oral administration may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration wherein the carrier is a solid are most preferably presented as unit dose formulations such as boluses, capsules or tablets each containing a predetermined amount of the active ingredients. A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compounds in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, lubricating agent, surface-active agent or dispersing agent. Moulded tablets may be made by moulding an inert liquid diluent. Tablets may be optionally coated and, if uncoated, may optionally be scored. Capsules may be prepared by filling the active ingredients, either alone or in admixture with one or more accessory ingredients, into the capsule shells and then sealing them in the usual manner. Cachets are analogous to capsules wherein the active ingredients together with any accessory ingredient(s) are sealed in

a rice paper envelope. The compound of formula (I) or a pharmaceutically acceptable salt or ester may also be formulated as dispersible granules, which may for example be suspended in water before administration, or sprinkled on food. The granules may be packaged e.g. in a sachet.

The active ingredients may also be formulated as a solution or suspension for oral administration. Formulations suitable for oral administration wherein the carrier is a liquid may be presented as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, or as an oil-in-water liquid emulsion.

As used herein, the term "prodrug" includes entities that have certain protected group(s) and which may not possess pharmacological activity as such, but may, in certain instances, be administered (such as orally or parenterally) and thereafter metabolised in the body to form the agents which are pharmacologically active.

Furthermore, the invention also provides a kit comprising in combination for simultaneous, separate or sequential use in modulating neoplastic growth, the compound according to formula (I) as defined above or a pharmaceutically acceptable salt, ester or prodrug thereof and an EGFR signalling pathway inhibitor.

Description of the Figures

Figure 1: shows the average tumour volume (relative to the average volume on the first day of treatment) for A549 (lung carcinoma) xenografts observed for an untreated control group of mice and for mice given (i.e. treated with) Erbitux™ (alone), DMXAA (alone), or a combination of Erbitux™ and DMXAA.

Figure 2: is a representation of the same data used to generate Figure 1, but expressed in terms of the percentage of mice having tumour volume less than four times the volume measured on the first day of treatment.

Examples

Example 1

Method

Xenografts for human lung cancer are set-up in groups of nude, athymic mice. The cell line selected was A549 (ATCC number CCL-185), a lung carcinoma.

The A549 was selected as DMXAA has previously been shown to be effective in these cell lines when used in combination with paclitaxel or 5-FU in xenograft studies.

Group	Cell line	Treatment	Dose level (mg/kg)	No. of mice
1	A549	Untreated control	-	10
2	A549	DMXAA	21	10
3	A549	Erbitux™	33*	10
4	A549	Erbitux™ / DMXAA	33* & 21	10

* Calculated from dose of 1 mg/mouse.

For this study, DMXAA is given twice in each of Weeks 1 and 4 of the study. Erbitux™ is given twice weekly for four weeks.

Xenografts are measured two or three times per week and their absolute volume recorded; xenograft tumour volume relative to that recorded on Day 0 (V_0) is then calculated. The time taken to reach a relative tumour volume of 3x V_0 is used as a surrogate marker for survival.

Results

Tables 1 and 2 below, as well as Figures 1 and 2 show that the combination of Erbitux™ and DMXAA provides an unexpected synergistic effect in delaying tumour growth.

Table 1. Results of studies with A549 xenografts.

Group	Dose (mg/kg by injection)	Drug deaths	Median VQT (Range; days)	Tumour Growth Delay[a] (Days)	Regression Duration[b] (Days)	TTP[c] (Days)
Erbitux™	33[d]	0/10	44	12	0	4
DMXAA	21	2/10	48	16	0	16
Erbitux™/ DMXAA	33[d] + 21	1/10	70	38	28	34

[a] The difference in days for treated versus control tumours to quadruple in volume (control tumours quadrupled in 17 (14 - 23) days).

[b] Tumour regression duration is the number of days that the tumour volume is less than the original treatment volume.

[c] TTP: Median time to disease progression.

[d] Calculated from dose of 1 mg/mouse.

Table 2. Results of studies with A549 xenografts.

Group	Dose (mg/kg by injection)	Response[e]			
		PD	PR	SD	CR
Erbitux™	33[d]	0/10	44	12	0
DMXAA	21	2/10	48	16	0
Erbitux™/ DMXAA	33[d] + 21	1/10	70	38	28

[d] Calculated from dose of 1 mg/mouse.

[e] PD: Progressive Disease (≥ 50% increase in tumour size)

PR: Partial Response (≥ 50% reduction in tumour size sustained over two weeks)

SD: Stable Disease (does not satisfy criteria for PR or PD)

CR: Complete Response (cure; undetectable tumour over two weeks)

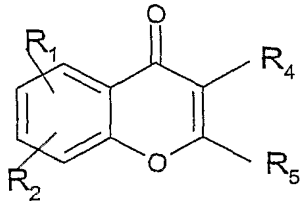
Abbreviations

AUC	=	area under curve (plasma concentration vs. time)
CR	=	Complete Response
DMXAA	=	5,6-dimethylxanthenoneacetic acid
EGF	=	endothelial growth factor
EGFR	=	endothelial growth factor receptor
ENL	=	erythema nodosum leprosum
5-FU	=	5-fluorouracil
HPC	=	hydroxypropylcellulose
HPMC	=	hydroxymethylcellulose
ICAM	=	intracellular adhesion molecule
i.p.	=	intraperitoneal
MRI	=	magnetic resonance imaging

PD	=	Progressive Disease
PK	=	pharmacokinetics
PR	=	Partial Response
SD	=	Stable Disease
TTP	=	median time to disease progression
VDA	=	vascular disrupting agent
VQT	=	(tumour) volume quadrupling time

CLAIMS

1. A method for modulating neoplastic growth, which comprises administering to a mammal, including a human, in need of treatment an effective amount of a compound of Formula (I):



Formula (I)

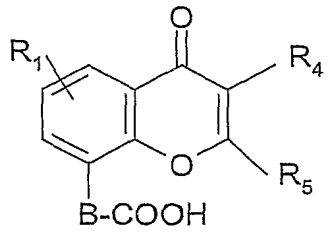
wherein:

(a) R_4 and R_5 together with the carbon atoms to which they are joined, form a 6-membered aromatic ring having a substituent $-R_3$ and a radical $-$(B)-COOH where B is a linear or branched substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated, and wherein R_1, R_2 and R_3 are each independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, CF_3, CN, NO_2, NH_2, OH, OR, NHCOR, $NHSO_2R$, SR, SO_2R or NHR, wherein each R is independently C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy; or

(b) one of R_4 and R_5 is H or a phenyl radical, and the other of R_4 and R_5 is H or a phenyl radical which may optionally be substituted, thenyl, furyl, naphthyl, a C_1-C_6 alkyl, cycloalkyl, or aralkyl radical; R_1 is H or a C_1-C_6 alkyl or C_1-C_6 alkoxy radical; R_2 is the radical -(B)-COOH where B is a linear or branched substituted or unsubstituted C_1-C_6 alkyl radical, which is saturated or ethylenically unsaturated,

or a pharmaceutically acceptable salt, ester or prodrug thereof and concomitantly or sequentially administering an EGFR signalling pathway inhibitor.

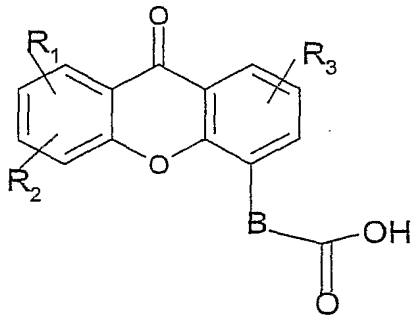
2. The method according to claim 1 wherein the compound of Formula (I) is a compound of Formula (II):



Formula (II)

wherein R_1, R_4, R_5 and B are as defined for formula (I) in claim 1 part (b).

3. The method according to claim 1 wherein the compound of Formula (I) is a compound of Formula (III):



Formula (III)

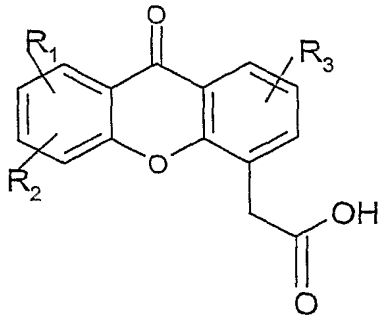
wherein R_1, R_2 and R_3 are each independently selected from the group consisting of H, C_1-C_6 alkyl, halogen, CF_3, CN, NO_2, NH_2, OH, OR, NHCOR, $NHSO_2R$, SR, SO_2R or NHR, wherein each R is independently C_1-C_6 alkyl optionally substituted with one or more substituents selected from hydroxy, amino and methoxy;

wherein B is as defined for formula (I) in claim 1;

and wherein in each of the carbocyclic aromatic rings in formula (I), up to two of the methine (-CH=) groups may be replaced by an aza (-N=) group;

and wherein any two of R_1, R_2 and R_3 may additionally together represent the group -CH=CH-CH=CH-, such that this group, together with the carbon or nitrogen atoms to which it is attached, forms a fused 6 membered aromatic ring.

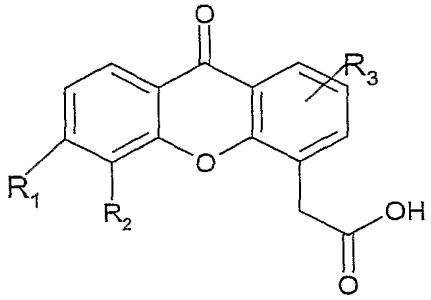
4. The method according to claim 3, wherein the compound of Formula (III) is a compound of Formula (IV):



Formula (IV)

wherein R, R_1, R_2 and R_3 are as defined for formula (III) in claim 3.

5. The method according to claim 4 wherein the compound of Formula (IV) is a compound of Formula (V):



Formula (V)

wherein R, R_1, R_2 and R_3 are as defined for formula (IV) in claim 4.

6. The method according to claim 1, wherein the compound of Formula (I) is DMXAA or a pharmaceutically acceptable salt, ester or prodrug thereof.

7. A method according to any one of Claims 1 to 6 wherein the compound of formula (I) or a pharmaceutically acceptable salt, ester or prodrug thereof and the EGFR signalling pathway inhibitor are administered concomitantly.

8. A method according to any one of Claims 1 to 6 wherein the compound of formula (I) or pharmaceutically acceptable salt, ester or prodrug thereof and the EGFR signalling pathway inhibitor are administered sequentially.

9. Use of a compound of formula (I), (II), (III), (IV) or (V), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, ester or prodrug thereof, for simultaneous, separate or sequential administration with an EGFR signalling pathway inhibitor for the modulation of neoplastic growth.

10. Use of an EGFR signalling pathway inhibitor for the manufacture of a medicament, for simultaneous, separate or sequential administration with a compound of formula (I), (II), (III), (IV) or (V), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, ester or prodrug thereof, for the modulation of neoplastic growth.

11. Use of a compound of formula (I), (II), (III), (IV) or (V), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, ester or prodrug thereof for the manufacture of a medicament, for simultaneous, separate or sequential administration with an EGFR signalling pathway inhibitor, for the modulation of neoplastic growth.

12. A pharmaceutical formulation comprising a combination of a compound of formula (I), (II), (III), (IV) or (V), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, ester or prodrug thereof and an EGFR signalling pathway inhibitor.

13. A pharmaceutical formulation according to Claim 12 wherein the formulation is adapted for intravenous or oral administration.

14. A pharmaceutical formulation according to Claims 12 or 13 which additionally comprises a pharmaceutically acceptable carrier.

15. A kit comprising in combination for simultaneous, separate or sequential use in modulating neoplastic growth, a compound a compound of formula (I), (II), (III), (IV) or (V), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, ester or prodrug thereof and an EGFR signalling pathway inhibitor.

16. The method of any one of Claims 1 to 8, the use of any one of Claims 9 to 11, the pharmaceutical formulation of any one of Claims 12 to 14, or the kit of Claim 15, wherein the EGFR signalling pathway inhibitor is a monoclonal antibody.

17. The method, use, pharmaceutical formulation or kit of Claim 16, wherein the EGFR signalling pathway inhibitor is Erbitux™ (cetuximab).

18. The method of any one of Claims 1 to 8, the use of any one of Claims 9 to 11, the pharmaceutical formulation of any one of Claims 12 to 14, or the kit of Claim 15, wherein the EGFR signalling pathway inhibitor is a tyrosine kinase inhibitor.

19. The method, use, pharmaceutical formulation or kit of Claim 18, wherein the EGFR signalling pathway inhibitor is Tarceva™ (erlotinib) or Iressa™ (gefitinib).

20. The method of any one of Claims 1 to 8, the use of any one of Claims 9 to 11, the pharmaceutical formulation of any one of Claims 12 to 14, or the kit of Claim 15, wherein the compound of formula (I) (II), (III), (IV) or (V), as defined in any one of Claims 1 to 6, is DMXAA or a pharmaceutically acceptable salt, ester or prodrug thereof.

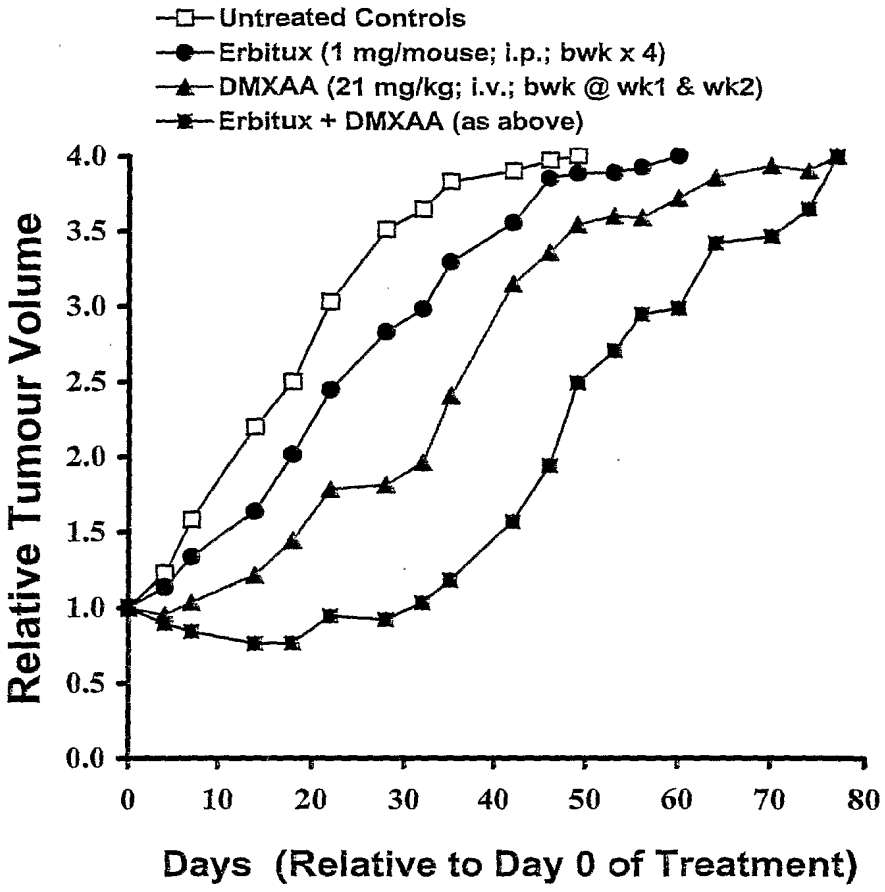

Untreated Controls
Erbitux (1 mg/mouse; i.p.; bwk x 4)
DMXAA (21 mg/kg; i.v.; bwk @ wk1 & wk2)
Erbitux + DMXAA (as above)
Relative Tumour Volume
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
50
60
70
80
Days (Relative to Day 0 of Treatment)

Fig. 1.

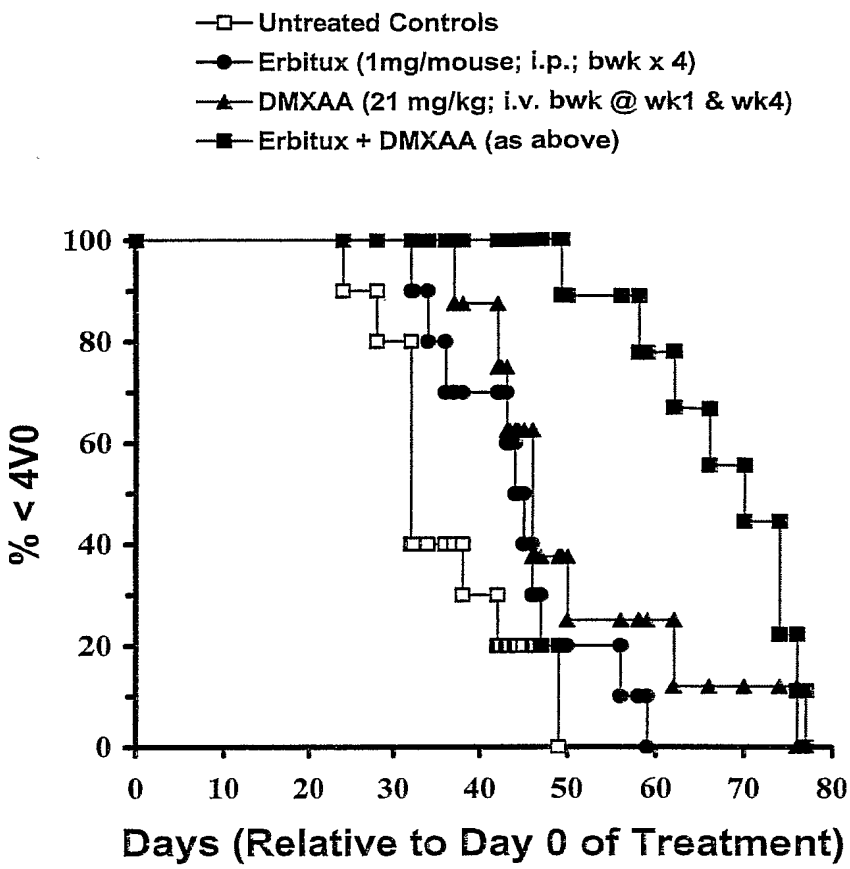

Untreated Controls
Erbitux (1mg/mouse; i.p.; bwk x 4)
DMXAA (21 mg/kg; i.v. bwk @ wk1 & wk4)
Erbitux + DMXAA (as above)
% < 4V0
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
Days (Relative to Day 0 of Treatment)

Fig. 2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003207

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/352 A61K39/395 A61K31/517 A61K31/5377 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/020259 A2 (CANCER REC TECH LTD [GB]; WILSON WILLIAM ROBERT [NZ]; SIIM BRONWYN GAE) 13 March 2003 (2003-03-13) page 18, line 29 - page 19, line 30 table 1 page 22, paragraph 2 - page 23	1-20
A	SIIM BRONWYN G ET AL: "Marked potentiation of the antitumour activity of chemotherapeutic drugs by the antivascular agent 5,6-dimethylxanthenone-4-acetic acid (DMXAA)." CANCER CHEMOTHERAPY AND PHARMACOLOGY. JAN 2003, vol. 51, no. 1, January 2003 (2003-01), pages 43-52, XP002411268 ISSN: 0344-5704 abstract	1-20

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 December 2006	29/12/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	RODRIGUEZ-PALMERO, M

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/003207

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BAGULEY BRUCE C ET AL: "Potential of DMXAA combination therapy for solid tumors." EXPERT REVIEW OF ANTICANCER THERAPY. OCT 2002, vol. 2, no. 5, October 2002 (2002-10), pages 593-603, XP009076041 ISSN: 1473-7140 the whole document	1-20
A	KELLAND LR: "Targeting Established Tumor Vasculature: A Novel Approach to Cancer Treatment" CURR. CANCER THER. REV., vol. 1, no. 1, January 2005 (2005-01), pages 1-9, XP002411269 ISSN: 1573-3947 page 5, column 1, paragraph 3 - page 6, column 2, paragraph 3	1-20

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/003207

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-9, 16-20 (in part) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/003207

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 03020259 A2	13-03-2003	BR	0212258 A	19-10-2004
		CA	2458459 A1	13-03-2003
		CN	1708296 A	14-12-2005
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		NO	20040591 A	30-04-2004
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